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(54) **Pharmaceutical controlled-release composition with bioadhesive properties**

Pharmazeutische Zusammensetzung mit kontrollierter Freigabe und bioadhäsiven Eigenschaften

Composition pharmaceutique à libération contrôlée à propriétés bioadhésives

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(56) References cited:

<b>EP-A- 0 330 532</b>	<b>EP-A- 0 387 782</b>
<b>EP-A- 0 452 268</b>	<b>WO-A-85/02092</b>
<b>WO-A-89/10117</b>	<b>FR-A- 2 497 098</b>

- **JOURNAL OF CONTROLLED RELEASE** vol. 13, no. 1, July 1990, AMSTERDAM pages 51 - 62;  
**LEHR C.-M. ET AL: 'Intestinal transit of bioadhesive microspheres in an in situ loop in the rat - a comparative study with copolymers and blends based on polyacrylic acid'**
- **PATENT ABSTRACTS OF JAPAN** vol. 12, no. 047 12 February 1988
- **LIST P.H. ET AL 'hagers handbuch der pharmazeutischen praxis' 1971, SPRINGER VERLAG, BERLIN HEIDELBERG NEW-YORK**
- **DEUTSCHE APOTHEKER ZEITUNG** vol. 130, no. 15, 12 April 1990, STUTTGART pages 791 - 801;  
**JUNGINGER H.E. ET AL: 'BIOADHÄSIVE ARZNEISTOFFABGABESYSTEME UND ARZNEIFORMEN FÜR PERORALE UND REKTALE ANWENDUNG'**

Remarks:

The file contains technical information submitted after the application was filed and not included in this specification

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**Description****FIELD OF THE INVENTION**

5 The present invention relates to a composition for the controlled release of medicinal drugs which has the additional property of adhering to biologic tissues, in particular to mucous membranes. The composition is designed for administration either by the oral route or other routes such as, for example, the nasal, rectal, vaginal, ocular and periodontal routes.

**BACKGROUND OF THE INVENTION**

10 The preparation of pharmaceutical compositions capable of ensuring a gradual and controlled release of active ingredients included therein has long been known to the pharmaceutical art. Known systems include tablets, capsules, microcapsules, microspheres and other dosage forms where the active ingredient is released gradually by various mechanisms.

15 These systems are intended to provide pharmaceutical dosage forms that can prolong the presence of the active ingredients in the subject to which they are administered at optimum plasma levels, thereby reducing the number of administrations required and improving patients' response to treatment.

20 It was recently observed that some drug bioavailability problems could be overcome by prolonging the presence of dosage forms at or near the locus within the host where their active ingredients are normally absorbed. These bioavailability problems stem from causes such as limited drug solubility (gastric or enteral), small absorption rate constant, or the presence of "windows" of absorption on (i.e. a limited time of absorption which stops upon saturation). Examples of such drugs (without limitation) include (i) carbamazepine (an antiepileptic), furosemide (a diuretic), metoprolol (a beta blocker) and acyclovir (an antiviral). Other drugs for which benefit from prolonged presence at or near the locus of absorption in terms of their bioavailability characteristics include drugs that act specifically on the gastrointestinal tract (e.g. aspirin) or which are absorbed most efficiently within the colon (e.g. peptides or proteins such as insulin, interferon, calcitonin, endorphins, human growth hormone, and various hormone growth factors).

25 From a theoretical point of view, an ideal solution of this problem can be found in formulation or dosage form materials with bioadhesive characteristics, bioadhesiveness being defined as the ability of a material (synthetic or biologic) to adhere to biologic tissues for a prolonged period of time. Although the length of this time cannot be given in terms of a numerical range that would apply to all drugs and all routes of administration, it is fair to describe such prolonged time period as a period of time (i) during which a drug is present at or near the locus of its absorption (ii) which is longer than the standard residence time for such drug (usually) not exceeding 8-10 hours for the gastrointestinal tract and up to about 24 hours).

30 In case of oral administration, normal or pathological stomach voiding and intestinal peristaltic movements may reduce the time for which a drug-releasing dosage form remains in contact with the mucous membrane responsible for absorption of the active ingredient. The rectal route of administration profits from the presence of the dosage form in the lower section of the rectum, where rectal veins make it possible to by-pass (and thereby overcome the effect of metabolism on the first passage through) the liver. Similar considerations apply to the ocular, vaginal, dental and nasal cavities, where spontaneous or ciliary movements may cause a premature elimination of a dosage form. The purpose of the bioadhesive is, therefore, to keep a pharmaceutical dosage form in an absorption site for an extended period of time. Naturally, release of effective amounts of the active ingredient must also be ensured throughout the bioadhesion period in order to attain this objective.

35 Some examples of bioadhesive materials used in controlled release formulations are already known.

40 International Patent Application No. WO 85/02092 discloses a bioadhesive pharmaceutical composition containing bioadhesive agents for skin and mucous membrane administration. The bioadhesive agents are fibrous, cross-linked and water-swelling polymers bearing carboxyl functional groups, which are, however, not water-soluble. This composition may consist of various dosage forms such as an "intimate mixture" of active ingredient and bioadhesive polymers, capsules, films or laminates. However, by the simple physical mixing process described in WO 85/02092 the active ingredient is simply dispersed in a bioadhesive polymer and the dispersion is placed in a capsule. There is no real bond between each drug-containing particle or granule and the bioadhesive substance and thus the contact area between active ingredient/bioadhesive and mucosa is always less than optimal, which causes clustering or clumping of the drug particles and the loss of the advantages imparted by the bioadhesive.

45 Another example is European Patent No. EP 205,282, which discloses a pharmaceutical controlled-release composition containing cellulose the composition being capable of adhering to mucous membranes. This composition is a solid dosage form and is confined to administration via the oral or nasal cavities. It consists of granules coated with muco-adhesive cellulose. These granules contain a pharmaceutical active ingredient, a long-chain aliphatic alcohol and water-soluble hydrous hydroxyalkylcellulose, the latter being used both as a granule ingredient and as an extra-granular

ingredient. In other words, the same polymer (cellulose) that is a significant constituent of the matrix responsible for release control is also the material relied upon for bioadhesiveness.

A third example is found in U.S. Patent No. 4,226,848, which discloses an administration method for a bioadhesive pharmaceutical composition. This method is said to ensure adhesion to the oral or nasal cavities of a pharmaceutical composition which includes a bioadhesive polymer matrix in which the active ingredient is suspended. In this case, the bioadhesive matrix is made up of both a cellulose ether and an acrylic acid homopolymer or copolymer.

Most of the above examples are characterized by the fact that release is controlled by means of the same material which ensures bioadhesion. This implies that, if bioadhesion characteristics are adjusted (for example by increasing or decreasing the amount of the bioadhesive material in the drug formulation), the release characteristics peculiar to a formulation will also be unintentionally affected and the effect may be undesirable (for example it might cause the rate of drug release to be faster or slower than would be appropriate). It is instead desirable to be able to manipulate dosage form adhesion while maintaining the release profile of the active ingredient(s) typical of a selected formulation and to modulate the release system in relation to the active ingredient while maintaining unchanged the bioadhesive properties of a formulation. Lehr C. M. et al. [Journal of Controlled Release, Vol. 13, pages 51-62, 1990, Lehr C. M., Bouwstra J. A., Tukker J.J., Junginger H.E., "Intestinal transit of bioadhesive microspheres in an *in situ* loop in the rats- A comparative study with copolymers and blends based on poly(acrylic acid)] studied the bioadhesive properties of beads of poly(2-hydroxyethyl methacrylate) [PHEMA] coated with swollen mucoadhesive polymers, such as Polycarcarbophil and Carbomer, by means of an air suspension process, without investigating drug delivery properties of the coated PHEMA beads. WO-A-8910117 discloses controlled release capsules or microcapsules comprising active ingredients encapsulated by salt sensitive shells coated with an adhesive system, prepared by including the capsules in an aqueous gel adhesive system. FR-A-2 497 098 discloses a two-layers tablet, comprising an adhesive layer made of a mixture of cellulose alkyl ether and polyacrylic acid and a non-adhesive layer, suitable for protecting lesions of oral mucous membrane, thus promoting wound healing without the aid of drugs.

EP-A-0 387 782 discloses controlled-release pharmaceutical compositions containing nifedipine, obtained by preparing solutions in organic solvents containing nifedipine, hydrophilic means and slow-releasing means, spreading said solutions onto inert supports, drying, sieving, mixing with excipients, and using the mixture thus obtained for preparing tablets or capsules.

EP-A-0 330 532 discloses compositions containing fenofibrate co-micronized with a solid surface-active agent, prepared by co-micronizing active ingredient and surface-active agent, adding lactose and amid, granulating in the presence of water, drying up to a water content of 1%, sieving the granules, adding magnesium stearate and polyvinylpyrrolidone, and filling capsules with the powder thus obtained.

PATENT ABSTRACT OF JAPAN (Vol. 12, No. 047 12, February 1988, JP-A-62 195 336) discloses pharmaceutical compositions for oral use obtained by blending calcitonin with an adhesive, swellable polymer and with fusidic acid.

## OBJECTS OF THE INVENTION

Accordingly, it is an object of the present invention to provide a controlled-release and bioadhesive pharmaceutical composition designed so that the function controlling release of the active ingredient(s) is independent of the function ensuring bioadhesion. It is thus possible to adapt (and optimize) the release-controlling function to any specific active ingredient and then, regardless of the nature of the active ingredient administered, to modulate bioadhesion to whichever extent best expresses the pharmacologic characteristics of the active ingredient, thus making it possible, for example, to increase the amount or to alter the type of bioadhesive without forcing a detrimental effect on the controlled-release characteristics.

The invention also allows appropriate modulation of the contact area between the locus of administration (e.g. mucous membrane) and the formulation so as to maximize bioadhesion and simultaneously increase the area available for drug absorption. The mass/exposed-surface ratio is much lower and more favorable to both release and adhesion than in the case of prior art tablets or large granules and, therefore, the contact surface between dosage form and locus of administration, which proportionally affects both bioadhesion and absorption, is very large.

These features of the composition which is an object of the present invention make it possible to administer the composition not only via the oral route, but - precisely due to the modulability of its components - also via the ocular, rectal, nasal, vaginal or periodontal routes, i.e. via any mucosa.

Another object of the invention is to provide an improved method for producing controlled-release drug compositions with bioadhesive properties.

## SUMMARY OF THE INVENTION

In particular, the present invention is directed to a controlled-release pharmaceutical composition in the form of bioadhesive granules having the ability of adhering to biologic tissues, said composition comprising

a) a multiplicity of controlled-release microunits, containing an active ingredient and at least one component which controls the release of the active ingredient in the environment, said component not substantially contributing to bioadhesive properties of said composition;

b) a bioadhesive coating for these microunits, comprising at least one physiologically acceptable bioadhesive polymer, said coating being applied by dry compression on the microunits, which are individually and thoroughly coated with the bioadhesive polymer, said bioadhesive coating being capable of ensuring adhesion of microunits to the tissues or membranes.

The present composition may contain an excipient which, depending on the route of administration selected, promotes delivery of the composition at the use point and/or permits retention of the pharmaceutical effectiveness of the composition during administration and at the use point.

Microunits which control release independently from the bioadhesive coating may comprise interchangeably controlled release matrices, reservoir or osmotic units, or biodegradable units. Advantageously, such units have an average diameter less than 1mm.

The small size of the microunits affords a larger area of contact between the bioadhesive coating and the larger tissue. The controlled-release characteristics are adjusted, if need be, by choice of type and amount of intragranular controlled-release agent. Bioadhesiveness is adjusted by choice and amount of bioadhesive coating. If the bioadhesive coating impedes controlled-release, the intragranular controlled-release agent is changed to counteract such impedance.

Bioadhesive coatings may be selected from coatings comprising at least one of a large variety of bioadhesive polymers. It is possible to modulate the bioadhesion force either by adjusting the quantity of bioadhesive applied on the microunits or by using mixtures of different polymers with the desired combination of bioadhesive characteristics. Preferably, the coating envelops each individual microunit completely and is bonded thereto.

In particular, the present composition may further comprise at least one extragranular physiologically acceptable excipient in contact with the outer surface of the bioadhesive coating.

The choice of (extragranular) excipient depends on the administration route, the objective being to deliver the bioadhesive controlled release microunits to the use point in optimal manner. In the case of oral administration, such excipients are selected from components which favor a fast and/or broad distribution of the microunits on the mucous membrane, e.g. which avoid clustering, often caused by excessive and rapid swelling of the bioadhesive component due to a poor choice of extragranular excipient.

Another aspect of the invention is directed to a method for coating controlled-release microunits with bioadhesive polymers comprising the following steps:

- a) mixing controlled-release microunits with a dry bioadhesive polymer or polymer mixture including at least one bioadhesive polymer;
- b) dry-compressing the mixture so obtained with the compression force required to bind said dry bioadhesive polymer or polymer mixture to the controlled-release microunits surface;
- c) crumbling the mass thus obtained so to form granules;
- d) sieving to obtain particles of the required size.

The present method may further comprise including physiologically acceptable extragranular excipients.

The method comprises dry-compression tableting without the aid of solvents and permits the quantity of bioadhesive combined with the microunits to be increased at will. It also permits coating of microunits with mixtures of polymers - bioadhesive or not - which could not be applied by conventional techniques.

## DETAILED DESCRIPTION OF THE INVENTION

### Controlled Release Microunits

The microunits a) which can be used for a controlled release of the drug include:

- reservoir units
- matrix units
- osmotic units
- biodegradable units.

(a) Reservoir units (which involve an inert permeable membrane having specific diffusion characteristics which encases the active agent or a composition containing the active agent) are used when an essentially constant rate of release needs to be achieved over a prolonged period of time (accomplished through the provision within the res-

ervoir of a saturated solution of the active agent) or when a first order release profile is desired (i.e. a decreasing rate of release caused by provision inside the unit of an unsaturated solution of the active agent).

(b) Matrix units (which involve active agents dispersed uniformly throughout a rate-controlling polymer matrix) generally have complex release profiles depending on the amount of active agent imbedded therein the solubility of this agent to the fluid of the larger locus, the nature of the rate-controlling polymer (or polymers) and the geometry of the device. Choice of matrix units is thus more complex than that of reservoir units.

(c) Osmotic units (which generally involve tablets containing the active agent which in turn has a given osmotic pressure; the tablets are coated with a membrane semipermeable to the active agent and have a small hole drilled through the membrane) are chosen when delivery of a saturated solution of the active agent is desired at an essentially constant rate (until the drug solution inside the coated tablet is no longer saturated).

(d) Biodegradable units (matrix units containing dispersed active agent which is released via a slow degradation of the matrix) are chosen when, for example, solubility of the active agent is very poor. The release characteristics of such units are determined by the points of the polymer matrix where hydrolytic degradation occurs, by whether degradation happens mostly or totally at the surface or mostly or totally uniformly throughout the matrix and by whether a diffusion system is superimposed on the matrix system.

These systems, which are used to control the release of the active ingredient, are thoroughly described in the literature and commonly used in the pharmaceutical art, and they are not in themselves an object of the present invention. A description of these systems can be found, for example, in the book by R. Baker: "Controlled release of biologically active agents", Ed: John Wiley and Sons, New York, 1978, pp. 38-153 incorporated by reference. Such systems are also commercially available, e.g. from Stolle, R&D Corporation, Cincinnati Ohio; or from Eurand Int'l S.p.A. Cinisello Balsamo, Milan, Italy.

The present invention permits selection, among various known systems, of the one which suits best the characteristics of the active ingredient to be administered and permits the system selected to be adapted to the peculiarities of the route of administration chosen. Such selection can readily be made by those of ordinary skill in the art. As a non-limiting example, the release of a very soluble active ingredient can be slowed down to the desired rate by using a hydrophobic matrix as the release-controlling component, and the release of a scantily soluble active ingredient can be speeded up by use of an osmotic unit as the release-controlling component, in either case without fear of adverse effect on bioadhesion.

Whatever unit is selected for controlling release, it is desirable that its size be within the following limits: Preferred unit size may vary within the range from 125 to 600 micrometers. However, acceptable size range may vary from 1 to 2,000 micrometers, subject to optimization (well within the skill of the art) depending on the type of active ingredient to be administered, the use point, the type of unit chosen for administration and the excipients used.

#### Active Ingredients

A large number of active ingredients may be administered more effectively by means of the bioadhesive controlled-release composition of the present invention. In particular, administration of active ingredients requiring constant concentrations in the host is particularly advantageous when performed in accordance with this invention.

The active ingredients which can be used may be selected without limitation among those belonging to the following groups: analgesics, antibacterials, antibiotics, anticonvulsants, antidepressants, antidiabetics, antifungals, antihistaminics, antihypertensives, anti-inflammatories, antiparkinsonian drugs, antipyretics, anticholinergic drugs, antimicrobials, antiviral drugs, antiulceratives, bronchodilators, cardiovascular drugs, contraceptives, decongestants, diuretics, hypoglycemics, hormones, ophthalmic drugs, hypnotics, sympathomimetic drugs, tranquilizers and vitamins.

Furosemide, terfenadine, calcitonin, pilocarpine, tetracycline (tetracycline hydrochloride) and naproxen are only some examples of active ingredients which can be administered by means of compositions formulated in accordance with the invention. Again, the foregoing drugs are listed for illustrative purposes only; subject to individual optimization, the invention is applicable to bioadhesive pharmaceutical compositions regardless of the active ingredient or active ingredients incorporated therein.

#### Polymers with Bioadhesive Characteristics

In accordance with the present invention, the microunits included in the pharmaceutical composition must be coated with bioadhesive polymers in order to interact with mucous membranes and adhere to them.

Many commercially available polymers already known in the literature (e.g., Smart, J.D. et al, *J. Pharm. Pharmacol.*, 1984, 36:295-99) as being bioadhesive can be used for this purpose. Examples (without limitation) include:

- polyacrylic polymers such as, carbomer and carbomer derivatives (Polycarbophyl, Carbopol etc);

- cellulose derivatives such as hydroxypropylmethylcellulose (HPMC), hydroxyethylcellulose (HEC), hydroxypropylcellulose (HPC) and sodium carboxymethylcellulose (NaCPC);
- natural polymers such as gelatin, sodium alginate, pectin;
- more generally, any physiologically acceptable polymer showing bioadhesive characteristics may be used successfully to coat controlled release units.

Bioadhesiveness can be determined *in vitro*, e.g. according to G. Sala et al., Proceed. Int. Symp. Contr. Release Bioact. Mat., 16: 420, 1989. See also WO 85/02092.

Suitable commercial sources for representative bioadhesive polymers include:

- Carbopol acrylic copolymer - BF Goodrich Chemical Co., Cleveland, OH, USA.
- HPMC - Dow Chemical Co., Midland, MI, USA.
- HEC (Natrosol) - Hercules Inc., Wilmington, DE, USA.
- HPC (Kluoel) - Dow Chemical Co., Midland, MI, USA.
- NaCMC - Hercules, Inc., Wilmington, DE, USA.
- Gelatin - Deamo Chemical Corp., Elmford, NY, USA.
- Sodium Alginate - Edward Mandell Co., Inc., Carmel, NY, USA.
- Pectin - BDH Chemicals Ltd., Poole Dorset, UK.
- Polycarbophil - BF Goodrich Chemical Co., Cleveland, OH, USA.

Although the weight ratio between controlled release units and bioadhesive polymer may vary between 5 and 0.1, the best results in terms of bioadhesive characteristics, low washability, and/or pharmaceutical properties and manufacturing technical and cost considerations are obtained with ratios of 2.5 to 0.25. While only one polymer may suffice for microunit coating, it was observed that, generally, a mixture of bioadhesive polymers with different characteristics yields better results. In particular, bioadhesive characteristics are more persistent when the coating is made of mixtures of acrylic polymers and cellulose derivatives.

Thus, for instance, mixtures of:  
carbomer/hydroxypropyl-methylcellulose,  
polycarbophil/ hydroxypropylmethyl-cellulose, or  
carbomer/hydroxypropylcellulose may be used to advantage in most administration situations.

Ratios between polymers showing more specific bioadhesive characteristics (e.g., an acrylic polymer) and any polymer acting at least predominantly as a binder (e.g., a cellulose derivative) may vary from about 0.2 to about 20. In most cases, optimum results are obtained using ratios of about 0.5 to about 5.

It should be noted that the final diameter of the coated particles may be from 1 to 2,500 micrometers, although it is generally preferable to limit the size to within the range of 300 to 600 micrometers.

#### Excipients

The excipients used to carry the pharmaceutical composition which is an object of the present invention in most of the customary routes of administration are those commonly known to the art. Examples can be found in Remington's 16th edition, Mack Publishing Co., Easton, PA, 1980, p. 1355.

In particular, in case of administration by the oral route, the bioadhesive controlled-release microunits are preferably carried within a hard gelatin capsule or a tablet, made in accordance with known techniques. However, microunits are inclined to adhere to each other and lose a large share of their release (and adhesion) characteristics when hydration and swelling of the coating of the microunits contained in the composition start before the microunits come out of the capsule or are released following tablet disintegration. In such a case, the microunits behave as any common single-dose dosage form (capsule or tablet) which does not disintegrate rapidly. The advantage of a large contact surface between mucous membrane and dosage form, which is typical of the microunits, is thus lost (E. Hunter et al., Int. J. Pharm., 17: 59 (1983)).

A particular composition was developed to prevent this condition and thus keep the particles separated. This formulation permits (inter alia) an oral administration of the composition which is an object of the present invention without incurring the above problems.

Said formulation, which is also an aspect of the present invention, is characterized by the inclusion of the following substances among the ingredients of the composition:

- a) at least a hydrophobic agent - such as, for instance, stearic acid and salts thereof such as magnesium stearate, calcium stearate, zinc stearate, talc, glyceryl fumarate, hydrogenated vegetable oils, polyethylene glycols, and other known compounds of similar behavior - which provide a protective coating on the bioadhesive particles thus delaying particle coating hydration;

b) at least a strong disintegrating agent which will speed up the exit of the microunits from the capsule or the disintegration of the tablet, and ensure dispersion of the bioadhesive microunits on the gastrointestinal mucous membrane.

Disintegrating agents include without limitation commercially available cross-linked polyvinylpyrrolidone, sodium carboxymethylstarch, sodium croscarmellose, starch, alginic acid, calcium carboxymethylcellulose, Guar gum, silicon dioxide, sodium alginate, and other known compounds of similar behavior.

The weight percentage in a formulation to be administered by the oral route may vary from about 1 to about 10% for the hydrophobic ingredient and from about 2 to about 20% for the disintegrating agent. Percentages are by weight based on the weight of the finished product.

#### Microunit Coating Method

There are two known processes for combining bioadhesive polymers and the active ingredient: mixing of polymers and the active ingredient and spray coating of the active ingredient in a fluid bed. However, these processes show various disadvantages when used to coat the microunits referred to in the present invention. Mixing will not permit individual coating of particles containing the active ingredient and will not provide sufficient force to firmly bind the coating to the microunits. Spray coating in a fluid bed involves excessively long processing times when the quantity of coating to be laid on the active ingredient-containing particle is high and, furthermore, it does not permit use of polymer mixtures if the constituent polymers of the mixture are only soluble in different solvents.

It has now been found, and this is also an aspect of the present invention, that a dry-tabletting method will permit the effective coating of microunits with bioadhesive polymers substantially free of one or both of the foregoing disadvantages.

According to this method, the microgranules are intimately mixed (using, e.g., a TURBULA mixer) with a bioadhesive polymer or with a mixture of polymers, including at least one bioadhesive polymer, and then compressed. The mass obtained by compression is then crumbled (e.g. by granulation) and the bioadhesive coated granules are sieved to obtain particles of the required size. Compression may be accomplished by any suitable means that would cause the bioadhesive coating to bind to the controlled-release microunit surface, such as a tabletting machine, or a compaction mill. The compression force used should preferably be the minimum required to bind the bioadhesive to the controlled-release microunit surface, but this is readily determined by those skilled in the art using no more than routine experiment. Usually, minimal average compression force values are within the range of about 0.5 to about 1 KN. As shown in the examples below, increase of the compression force does not affect the properties of the present invention.

A microscopic examination will show that all the microunits coated by the dry-compression method described above are individually and thoroughly coated with bioadhesive polymers.

Another advantage of this method is that the compression force and subsequent crumbling do not significantly affect the desirable release characteristics of the bioadhesive granules. This makes the method flexible. The method is also suitable for use with a wide variety of materials and active ingredients.

By this method, it is, for instance, easy to coat even single i.e. individual microunits with relatively large quantities of bioadhesive polymer (e.g., up to ten times of the weight of the "naked" controlled-release microunit) that can be compression-bound to the surface. Since increasing the quantity of a bioadhesive polymer will increase the strength of bioadhesion, it is possible to modulate total dosage form adhesion and adapt it in a simple and economic way to the requirements of the drug to be administered. If the amount and nature of the bioadhesive coating is such that it will impede release rate, a faster release unit can be provided to perform the release control function.

The following examples will describe the invention and its advantages in detail, in particular with regard to the materials, techniques and active ingredients used.

The examples were carried out using the following equipment: TURBULA® mixer (Willi A. Bachofen AG Basel, Switzerland), TONAZZI® kneader (Tonazzi vittorio e C. srl, Milan, Italy), ERWEKA® granulator (Erweka GmbH Heusenstamm, Germany), SILVERSON® turboemulsifier (Silversten Ltd., Chesham, U.K.), RONCHI® eccentric press (Officine Meccaniche Fratelli Ronchi, Cinisello Balsamo, Milan, Italy) WURSTER-GLATT® fluid-bed system (Glatt GmbH Binzen-Lörrach, Germany).

#### EXAMPLE 1: Bioadhesive Granules With Matrix Units for the Controlled Release of Furosemide

##### a) Hydrophobic Matrix Obtained by Granulation with Melted Excipients

50 parts of furosemide are mixed with 25 parts of hydrogenated castor oil and the resulting mixture is kneaded using 25 parts of melted hydrogenated castor oil as a granulation fluid. The resulting mixture is then granulated to obtain granules with a diameter of 125 to 500 microns. 33 parts of the granules obtained are mixed with 33 parts of an acrylic copolymer (Carbopol® 934 - Goodrich Chemical Co.) and 33 parts of hydroxypropylmethylcellulose with a vis-

cosity of 4000 cps in 2% water solution (Methocel® E4M - Dow Chemical Co.). The mixture is then tabletted in an eccentric press using a compression force of 8 KiloNewtons (KN), obtaining tablets with a diameter of 21 mm. The tablets are then crumbled and sieved so as to obtain granules with a diameter of 300 to 600 microns.

b) Matrix With Intermediate Hydrophobicity Obtained by Granulation With Melted Excipients

25 parts of furosemide are mixed with 25 parts of hydrogenated castor oil and 25 parts of calcium phosphate. The mixture is kneaded using 25 parts of melted hydrogenated castor oil as a fluid binder. The resulting mixture is then granulated to obtain granules with a diameter of 125 to 500 microns. 33 parts of the granules obtained are mixed with 33 parts of an acrylic copolymer (Carbopol® 934 - Goodrich Chemical Co.) and 33 parts of hydroxypropylmethylcellulose with a density of 4000 cps (Methocel® E4M - Dow Chemical Co.). The mixture is then tabletted in an eccentric press using a compression force of 8 KN, obtaining tablets with a diameter of 21 mm. The tablets are then crumbled and sieved so as to obtain granules with a diameter of 300 to 600 microns.

EXAMPLE 2.: Bioadhesive Granules with Reservoir Units For the Controlled Release of Furosemide

a) Reservoir Unit with a 0.5 Nucleus/Bioadhesive-Polymer Ratio

50 parts of furosemide are kneaded with 47.5 parts of lactose and 2.5 parts of a 10% aqueous solution of polyvinyl alcohol as a fluid binder. The resulting mixture is then dried in a forced ventilation oven at 50°C for 3 hours and granulated to obtain granules with a diameter of 125 to 600 microns. The controlled release of the active ingredient is achieved by coating 85 parts of the granules obtained in a fluid-bed system using as a coating agent 15 parts of a polymer film which has the following composition:

glyceryl monostearate	13.50 (parts)
beeswax	1.20
stearyl alcohol	0.15
cetyl alcohol	0.15

33 parts of the granules so coated are mixed with 33 parts of Carbopol® 934 and 33 parts of Methocel® E4M. The mixture is then tabletted in an eccentric press using a compression force of 8 KN, obtaining tablets with a diameter of 21 mm. The tablets are then crumbled and sieved so as to obtain granules with a diameter of 300 to 600 microns.

b) Reservoir Unit With a Nucleus/Bioadhesive-Polymer Ratio of 0.25

Bioadhesive granules containing furosemide in reservoir nuclei are prepared in accordance with the method described in Example 2a), as far as the release-controlling nucleus is concerned. 20 parts of granules so prepared and coated are mixed with 40 parts of Carbopol® 934 and 40 parts of Methocel® E4M. The mixture is then tabletted in an eccentric press using a compression force of 8 KN, obtaining tablets with a diameter of 21 mm. The tablets are then crumbled and sieved so as to obtain granules with a diameter of 300 to 600 microns.

EXAMPLE 3. Bioadhesive Granules With Reservoir Units for the Controlled Release of Terfenadine

a) Reservoir Nucleus With Low Hydrophilic Properties

50 parts of terfenadine are mixed with 47 parts of calcium monohydrogen phosphate. The mixture is kneaded using 3 parts of a 10% aqueous solution of polyvinyl alcohol as a fluid binder. Mixture processing, granulation, granule coating with a film capable of controlling the release and further coating with Carbopol 934 and Methocel® E4M, follow the method described in Example 2a). Here again granules with a diameter of 300 to 600 microns are obtained.

b) Reservoir Nucleus with High Hydrophilic Properties

50 parts of terfenadine are mixed with 47 parts of lactose. The mixture is kneaded using 3 parts of a 10% aqueous solution of polyvinyl alcohol as a fluid binder. Mixture processing, granulation and granule coating with a film capable of controlling the release follow the method described in Example 2a). 50 parts of the granules so coated are mixed with 25 parts of Carbopol® 934 and 25 parts of Methocel® E4M. The mixture is then tabletted in an eccentric press using



a compression force of 8 KN, obtaining tablets with a diameter of 21 mm. The tablets are then crumbled and sieved so as to obtain granules with a diameter of 300 to 600 microns.

c) Reservoir Nucleus with Intermediate Hydrophilic Properties

50 parts of terfenadine are mixed with 27 parts of calcium monohydrogen phosphate and 20 parts of lactose. The mixture is kneaded using 3 parts of a 10% aqueous solution of polyvinyl alcohol as a fluid binder. Mixture processing, granulation and granule coating with a film capable of controlling the release follow the method described in Example 2a). 33 parts of the granules so coated are mixed with 33 parts of Carbopol® 934 and 33 parts of Methocel® E4M. The mixture is then tabletted in an eccentric press using a compression force of 8 KN, obtaining tablets with a diameter of 21 mm. The tablets are then crumbled and sieved so as to obtain granules with a diameter of 300 to 600 microns.

EXAMPLE 4.: Bioadhesive Granules with Biodegradable Units for the Controlled Release of Calcitonin

An aqueous solution is prepared with 50 parts of calcitonin and 50 parts of albumin. This solution is then emulsified in cotton-seed oil with the aid of sorbitan trioleate (Span® 85 available from ICI Imperial Chemical Industries). A fine and homogeneous dispersion of the aqueous phase in the fatty phase is obtained using a turboemulsifier. 2,3-butanedione is then added to the emulsion to permit albumin cross-linking. This emulsion is then repeatedly diluted with ether to replace most of the fatty phase. The microcapsules so obtained are collected by centrifugation and dried. 33 parts of these microcapsules are mixed with 33 parts of Carbopol® 934 and 33 parts of Methocel® E4M. The mixture is then tabletted in an eccentric press using a compression force of 1.5 KN, obtaining tablets with a diameter of 21 mm. The tablets are then crumbled and sieved so as to obtain granules with diameters of 100 to 200 microns.

EXAMPLE 5.: Bioadhesive Granules with Osmotic Units for the Controlled Release of Naproxen

50 parts of naproxen are kneaded with 47.5 parts of mannitol and 2.5 parts of a 10% aqueous solution of polyvinyl alcohol as a fluid binder. The mixture so obtained is then dried in a forced ventilation oven at 50°C for 3 hours and granulated to obtain granules with a diameter of 125 to 600 microns. In order to control naproxen release, the nuclei are coated with a semi-permeable membrane, which is made porous by the presence of water-soluble material (polyethylene glycol). 85 parts of granules are coated in a fluid bed system using as a coating agent 15 parts of a polymer film with the following composition:

cellulose acetate	90 parts
polyethylene glycol	10 parts

33 parts of the granules so coated are mixed with 33 parts of Carbopol® 934 and 33 parts of Methocel® E4M. The mixture is then tabletted in an eccentric press using a compression force of 8 KN, obtaining tablets with a diameter of 21 mm. The tablets are then crumbled and sieved so as to obtain coated granules with a diameter of 300 to 600 microns.

EXAMPLE 6.: Bioadhesive Granules with Biodegradable Units For the Controlled Release of Tetracycline Hydrochloride

30 parts of tetracycline hydrochloride and 70 parts of poly(L-lactate/glycolate) (1/1) copolymer are dispersed by stirring in dichloromethane. This dispersion is emulsified in a 4% aqueous solution of polyvinyl alcohol in a turboemulsifier. The use of a turboemulsifier permits microcapsules of adequately small size to be obtained. The vessel containing the emulsion is set at 37°C for 4 hours in order to allow evaporation of dichloromethane. During this operation, the emulsion is constantly stirred. After 4 hours, the microcapsules are separated by filtration, washed in cold water and then dried in an air circulating oven at 40°C for 24 hours. 50 parts of the microcapsules are mixed with 25 parts of Carbopol® 934 and 25 parts of Methocel® E4M. The mixture is then tabletted in an eccentric press using a compression force of 1.5 KN, obtaining tablets with a diameter of 21 mm. The tablets are then crumbled and sieved so as to obtain coated granules with a diameter of 50 to 200 microns.

EXAMPLE 7.: Bioadhesive Granules with Biodegradable Units For the Controlled Release of Pilocarpine

5 parts of pilocarpine and 95 parts of poly(L-lactate/glycolate) (1/1) copolymer are dispersed in dichloromethane by constant stirring. This dispersion is then emulsified in a 4% aqueous solution of polyvinyl alcohol. Stirring is adjusted so as to obtain a very fine and homogeneous dispersion of the organic phase in the aqueous phase. The emulsion is

then placed in a temperature-controlled bath set at 37°C and stirred for 4 hours in order to let all the dichloromethane evaporate. After cooling, the microcapsules are separated by filtration and washed with cold water. The washed microcapsules are dried for 24 hours in an air circulating oven at 40°C. 50 parts of the microcapsules so obtained are mixed with 25 parts of Carbopol® 934 and 25 parts of Methocel® E4M. The mixture is then tableted in an eccentric press using a compression force of 1.5 KN, obtaining tablets with a diameter of 21 mm. The tablets are then crumbled and sieved so as to obtain granules with a diameter smaller than 10 microns.

EXAMPLE 8.: Release of Granules from a Hard-Gelatine Capsule for Oral Administration

This example emphasizes the role played by the excipients (disintegrating agent and hydrophobic agent) added to a composition for oral administration. Various formulations were tested in order to evaluate the efficacy of various disintegrating agents combined with magnesium stearate.

A hard-gelatine capsule No. 3 containing the bioadhesive controlled release granules (containing furosemide and prepared as described in Example 1 a)) and the other excipients is held on the bottom of a dissolution vessel filled with 37°C water and stirred by rotating at 20 rpm. The capsule is removed from the vessel at pre-established intervals and the water is filtered in order to recover any released granules. The exact quantity of granules released is determined by assaying the active ingredient.

Capsule A

Bioadhesive controlled-release granules without excipients.

Capsule B

95 parts of bioadhesive controlled-release granules and 5 parts of magnesium stearate.

Capsule C

95 parts of bioadhesive controlled-release granules and 5 parts of croscarmellose sodium.

Capsule D

90 parts of bioadhesive controlled-release granules, 5 parts of magnesium stearate and 5 parts of croscarmellose sodium.

Capsule E

85 parts of bioadhesive controlled-release granules, 5 parts of magnesium stearate and 10 parts of croscarmellose sodium.

Capsule F

80 parts of bioadhesive controlled-release granules, 5 parts of magnesium stearate and 15 parts of croscarmellose sodium.

Capsule G

90 parts of bioadhesive controlled-release granules, 5 parts of magnesium stearate and 5 parts of cross-linked polyvinylpyrrolidone.

Capsule H

85 parts of bioadhesive controlled-release granules, 5 parts of magnesium stearate and 10 parts of cross-linked polyvinylpyrrolidone.

Capsule I

90 parts of bioadhesive controlled-release granules, 5 parts of magnesium stearate and 5 parts of carboxymethyl-starch.

TABLE 1

Time (min)	% Granules Released								
	A	B	C	D	E	F	G	H	I
2	0	0	0	0	0	0	0	20	0
5	0	0	0	0	10	50	0	80	0
10	0	5	5	15	30	65	20	100	5
15	0	5	10	20	35	75	30	100	5
20	0	15	15	35	50	80	70	100	15
25	FOC	40	30	75	85	90	100	100	50
30	FOC	50	50	95	95	100	100	100	85
35	FOC	50	60	100	100	100	100	100	100
"FOC" means formation of clumps, evaluated by visual inspection.									

The figures shown in Table 1 evidence that the simultaneous presence in the capsule, together with the bioadhesive controlled release granules, of a hydrophobic agent and a disintegrating agent can speed up the exit of the granules (capsules D-I). The presence of a hydrophobic agent alone (capsule B) or a disintegrating agent alone (capsule C) is not sufficient to cause all the bioadhesive granules to come out of the capsule within the period of time considered appropriate (0 - 35 min). The example combination showing the best results is that of capsule H, but capsules D through I and especially capsules E-H gave excellent results.

#### EXAMPLE 9.: Bioadhesive Composition for the Controlled Release of Pilocarpine in the Eye

60 parts of bioadhesive granules for the controlled release of pilocarpine, which are prepared as described in Example 7, are dispersed in 40 parts of a saline isotonic solution immediately before instillation. The isotonic suspension is instilled into the eye. The results will show prolonged release of pilocarpine compared to non-bioadhesive formulations.

#### EXAMPLE 10.: Bioadhesive Composition for the Controlled Release of Calcitonin in the Nasal Cavity

65 parts of bioadhesive granules for the controlled release of calcitonin, which are prepared as described in Example 4, are dispersed in 35 parts of a 2% aqueous solution of polyvinylpyrrolidone immediately before instillation. The resulting suspension is instilled into the nasal cavity. The results will show prolonged release of calcitonin compared to conventional formulations.

#### EXAMPLE 11.: Bioadhesive Composition for the Controlled Release of Tetracycline Hydrochloride in the Periodontal Cavity

23 parts of bioadhesive granules for the controlled release of tetracycline, which are obtained as described in Example 6, are mixed with 2 parts of tetracycline hydrochloride. This antibiotic fraction will provide a readily soluble dose. The mixture of bioadhesive granules and free tetracycline hydrochloride is mixed with 75 parts of 35% poloxamer gel. The gel containing bioadhesive granules and free tetracycline is injected into the periodontal cavity by a syringe equipped with a suitable needle. The results will show prolonged release of tetracycline compared to conventional formulations.

#### EXAMPLE 12.: Bioadhesive Composition for the Controlled Release of Naproxen in the Vagina or in the Rectum

25 parts of bioadhesive granules for the controlled release of naproxen, which are obtained as described in Example 5, are dispersed in 75 parts of mygliol® 810 (a hydrophobic liquid vehicle available from Dynamit Nobel Aktieng. 5 Cologne 80 Wiener platz Germany) and stirred for 15 minutes in a stainless steel reactor. The following compounds which make up the shell are placed in another stainless steel vessel: gelatine 65 parts, glycerin 33 parts, titanium dioxide 1 part, sodium methylparaoxybenzoate 0.5 parts and sodium propylparaoxybenzoate 0.5 parts. These compounds are melted at 70°C and stirred for 15 minutes. The melted shell mixture is introduced into a Scherer® capsule filling machine. Soft gelatine capsules of appropriate shape and size are produced and the dispersion of bioadhesive gran-

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ules in mygliol® 810 is injected into the suppositories by means of suitable needles. The results will show prolonged release of naproxen compared to commercially available formulations.

### EXAMPLE 13.: Dissolution Profile of the Bioadhesive Granules Obtained as per Examples 1 and 2

Dissolution tests were carried out in accordance with the following test conditions:

apparatus: II USP Ed. XXII, Apparatus II pp. 1578-1579

dissolution medium: phosphate buffer pH 5.9 - 900 ml

temperature: 37°C

stirring speed: 50 rpm

detection: UV absorption of 282 nm

TABLE 2

Time (hours)	% Furosemide Released			
	Example 1a	Example 1b	Example 2a	Example 2b
0	0	0	0	0
1	25.1	26.2	28.0	16.0
2	37.3	36.2	48.2	36.8
4	48.6	46.4	57.2	49.6
8	60.3	58.2	71.5	61.3
12	67.1	66.2	83.5	71.4
18	72.3	71.0	93.1	84.4
24	77.3	79.3	99.6	94.8

The table shows that the same active ingredient can have different release profiles when different components and microunits are used

### EXAMPLE 14.: Dissolution Profile of the Bioadhesive Granules Obtained as per Example 3

Dissolution tests were carried out in accordance with the following test conditions:

apparatus: II USP Ed. XXII as per Ex. 13.

dissolution medium: 0.1 N HCl - 900 ml

temperature: 37°C

stirring speed: 50 rpm

determination: HPLC (high performance liquid chromatography)

column: Novapack C18

mobile phase: acetonitrile = 60

acetate buffer pH 4.5 = 40

flow: 1.2 ml/min

detector: UV 225 nm

temperature: 25°C

internal standard: nortriptyline

TABLE 3

Time (hours)	% Terfenadine Released		
	Example 3a	Example 3b	Example 3c
0	0	0	0
1	31.0	43.9	37.6
2	46.1	59.7	50.5
4	55.5	71.9	66.5
8	67.5	84.3	84.2
12	76.1	91.6	91.4
18	84.0	97.9	98.4
24	92.9	100.0	100.0

In all the Table 3 formulations the active ingredient is released in a controlled way over 24 hours.

#### EXAMPLE 15.: Evaluation of Bioadhesive Properties

To evaluate in vitro the bioadhesive properties of the formulations which are an object of the present invention, a method permitting evaluation of bioadhesive properties directly on finished dosage forms (G. Sala et al., Proceed. Int. Symp. Contr. Rel. Bioact. Mat. 16:420, 1989) was used. (A tensile tester made by INSTRON, Canton, MA is also a suitable apparatus for assessing bioadhesive strength.) This evaluation was based on measurements of the flow of water required to remove the granules from the intestinal mucous membrane of a rabbit. A strip of rabbit mucous membrane is placed horizontally in a suitable temperature-controlled chamber set at 37°C. The tissue is first washed with predetermined volumes of water (e.g. 20-30 ml) by means of a peristaltic pump. An exact quantity of granules by weight (e.g. 5-15 mg) is then placed on the tissue and allowed to stand for 2 minutes to ensure proper hydration of the granule bioadhesive coat. The granules are then eluted with water pumped by a peristaltic pump for 10 minutes. The washed-away granules are collected and the active ingredient content is determined by U.V. assay in order to establish the exact percentage of particles removed. Subsequent tests are carried out using increasing eluting flows. The results are shown in Table 4, where the percentages of removal at the different water flows are listed respectively for:

- A: granules containing furosemide with no coating of bioadhesive material (average diameter 300 -500 microns);
- B: granules containing furosemide prepared as described in Example 1a (average diameter 400 -600 microns).

TABLE 4

Flow (ml/min)	% Granules Removed	
	A	B
6.0	76.9	0.0
7.1	88.1	0.0
15.7	100.0	17.9
17.7	100.0	26.6
19.8	100.0	33.5
21.7	100.0	39.7

From Table 4, it is evident that under the same elution conditions, the presence of a bioadhesive coating will significantly reduce the quantity of granules removed from the mucous membrane.

**EXAMPLE 16: Effect of Changing the Bioadhesive Coat Thickness on Units for the Controlled Release of Furosemide**

A demonstration of the effect of the bioadhesive coating thickness on dissolution and bioadhesion values was obtained preparing 3 different formulations using the controlled-release nucleus described in Example 2a), but changing the proportions of the ingredients which make up the bioadhesive coating of Example 2a):

Formulation A:	
Controlled release granules	50 parts
Acrylic acid copolymer	25 parts
Hydroxypropylmethylcellulose	25 parts
Formulation B:	
Controlled release granules	33 parts
Acrylic acid copolymer	33 parts
Hydroxypropylmethylcellulose	33 parts
Formulation C:	
Controlled release granules	20 parts
Acrylic acid copolymer	40 parts
Hydroxypropylmethylcellulose	40 parts

TABLE 5

Comparative Dissolution of Formulations A, B and C			
Time (hours)	% Furosemide Dissolved		
	A	B	C
1	36.4	28.0	16.0
2	54.1	48.2	36.8
3	62.7	56.2	45.7
5	73.2	63.0	53.0
8	82.7	71.5	61.3
12	88.7	83.5	71.4
18	91.9	93.1	84.4
24	93.3	99.6	94.8

TABLE 6

Comparative Evaluation of the Bioadhesive Properties of Formulations A, B and C			
Flow (ml/min)	% Granules Removed		
	A	B	C
15.7	17.3	12.2	4.5
17.7	25.6	13.5	6.4
19.8	33.0	16.7	8.9
21.7	39.0	17.2	11.2

The Table 5 and 6 data show that it is possible to improve bioadhesion by increasing the thickness of the bioadhesive coat without significantly affecting the dissolution profile of the active ingredient. This in turn means that in accordance with the invention each of bioadhesion and release control can be modulated separately without substantial mutual influence.

**EXAMPLE 17: Effect of Changing the Bioadhesive Coat Thickness on Microunits for the Controlled Release of Terfenadine**

A demonstration of the effect of the bioadhesive coating thickness on dissolution and bioadhesion values was obtained preparing three different formulations the controlled-release nucleus of which was prepared as described in Example 3a), but the proportions of the ingredients which make up the bioadhesive coating were changed in accordance with the same method described in Example 16 (formulations D, E and F):

TABLE 7

Comparative Dissolution of Formulations D, E and F			
Time (hours)	% Terfenadine Released		
	D	E	F
1	36.5	31.5	34.6
2	47.2	46.1	50.5
4	60.5	55.5	62.5
8	71.3	67.5	74.2
12	83.9	76.1	81.4
18	88.0	84.0	89.5
24	95.0	92.9	98.1

TABLE 8

Comparative Evaluations of the Bioadhesive Properties of Formulations D, E and F			
Flow (ml/min)	% Granules Removed		
	D	E	F
11.4	17.6	0.0	0.0
15.7	19.1	7.6	5.5
19.8	31.1	11.6	6.3
21.7	35.1	16.5	12.1

Again, Table 7 and 8 data show that it is possible to improve bioadhesion by increasing the thickness of the bioadhesive coat without significantly affecting the dissolution profile of the active ingredient.

#### EXAMPLE 18: Effects of the Compression Force and Crumbling Method

The bioadhesive and dissolution properties of the present invention are not dependent on the compression force used for dry coating the controlled release units with bioadhesive polymers and are equally not dependent on the crumbling method used.

To prove this, three formulations were prepared as described in Example 2a. These formulations contained furosemide and differed from each other either because of a different compression force used during compression of the bioadhesive polymers or because of the crumbling method:

Formulation G:

Compression force used 1.5 KN  
Mechanical crumbling by an Erweka apparatus

Formulation H:

Compression force used 7 KN  
Mechanical crumbling by an Erweka apparatus

Formulation I:

Compression force used 7 KN  
Gentle crumbling by hand in a mortar

TABLE 9

Dissolution of Formulations G, H and I			
Time (hours)	% Furosemide Released		
	G	H	I
1	37.6	36.5	35.9
2	47.3	45.2	49.3
4	60.7	60.6	62.9
8	79.3	76.3	80.3
12	92.5	93.9	94.7
18	100.0	100.0	100.0



TABLE 10

Evaluation of the Bioadhesive Properties of Formulations G, H and I			
Flow (ml/min)	% Granules Removed		
	G	H	I
13.7	4.2	5.7	5.3
15.7	6.5	6.9	7.1
19.8	9.0	11.1	10.8

The Table 10 data show how small are the differences in dissolution and bioadhesion values observed when changing either the compression force or the crumbling method.

### Claims

Claims for the following Contracting States : AT, BE, CH, LI, DE, DK, FR, GB, IT, LU, MC, NL, PT, SE

1. A controlled-release pharmaceutical composition in the form of bioadhesive granules having the ability of adhering to biologic tissues, said composition comprising
  - a) a multiplicity of controlled-release microunits, containing an active ingredient and at least one component which controls the release of the active ingredient in the environment, said component not substantially contributing to bioadhesive properties of said composition;
  - b) a bioadhesive coating for these microunits, comprising at least one physiologically acceptable bioadhesive polymer, said coating being applied by dry compression on the microunits, which are individually and thoroughly coated with the bioadhesive polymer, said bioadhesive coating being capable of ensuring adhesion of microunits to the tissues or membranes.
2. The composition according to claim 1, wherein said composition further comprises at least one extragranular physiologically acceptable excipient in contact with the outer surface of the bioadhesive coating.
3. The composition according to claim 1, wherein said controlled-release microunits are selected from reservoir units, matrix units, osmotic units, biodegradable units and combination thereof.
4. The composition according to claim 1, wherein said controlled-release microunits have a size within the range from 125 to 2,000 micrometers.
5. The composition according to claim 4, wherein said range is from 125 to 600 micrometers.
6. The composition according to claim 1, wherein said bioadhesive polymer is selected from polyacrylic polymers, acrylic copolymers, cellulose derivatives, natural polymers having bioadhesive properties, and mixtures thereof.
7. The composition according to claim 6, wherein the bioadhesive polymer is selected from carbomers, carbomer derivatives, polycarbophyl, hydroxypropylmethylcellulose, hydroxyethylcellulose, hydroxypropylcellulose, sodium carboxymethylcellulose, gelatin, sodium alginate, pectin and mixtures thereof.
8. The composition according to claim 1, wherein said coating comprises said bioadhesive polymer and a second polymer acting as a binder.
9. The composition according to claim 8, wherein the weight ratio of said bioadhesive polymer to said binder is within the range of 0.2 and 20.
10. The composition according to claim 9, wherein said range is between 0.5 and 5.
11. The composition according to claim 8, wherein the bioadhesive polymer is an acrylic polymer and the binder is a cellulose derivative.

12. The composition according to claim 11, wherein said coating is made of mixtures of acrylic polymers and cellulose derivatives selected from mixtures carbomer/hydroxypropyl-methylcellulose, mixtures polycarbophil/hydroxypropyl-methylcellulose and mixtures carbomer/hydroxypropyl-cellulose.
- 5 13. The composition according to claim 1, wherein the weight ratio of said microunits to the bioadhesive polymer is within the range between 5 and 0.1.
14. The composition according to claim 13, wherein said range is between 2.5 and 0.25.
- 10 15. The composition according to claim 1, wherein the final diameter of the coated microunits is within the range between 1 and 2,500 micrometers.
16. The composition of claim 15, wherein said range is between 300 and 600 micrometers.
- 15 17. The composition according to claim 2, being suitable for oral administration, wherein said excipients comprise at least one hydrophobic agent, which delays hydration of the bioadhesive coating, and at least one disintegrating agent, which promotes dispersion of the bioadhesive microunits over the gastrointestinal mucous membrane.
- 20 18. The composition according to claim 17, wherein the hydrophobic agent is selected from stearic acid, magnesium stearate, calcium stearate, zinc stearate, talc, glyceryl fumarate, hydrogenated vegetable oils and polyethylene glycols.
- 25 19. The composition according to claim 17, wherein the disintegrating agent is selected from cross-linked polyvinylpyrrolidone, sodium carboxymethylstarch, sodium croscarmellose, starch, alginic acid, calcium carboxymethylcellulose, guar gum, silicon dioxide and sodium alginate.
- 30 20. The composition of claim 17, wherein the weight percentage of the hydrophobic agent is within the range of 1 to 10% and that of the disintegrating agent is within the range of 2 to 20%, said weight percentages being based on the weight of the finished product.
- 35 21. The composition according to claim 1, wherein the active ingredient is selected from analgesic, antibacterial, antibiotic, anticonvulsant, antidepressant, antidiabetic, antifungal, antihistaminic, antihypertensive, antiinflammatory, antiparkinsonian, antipyretic, anticholinergic, antimicrobial, antiviral, antiulcerative, bronchodilating, cardiovascular, contraceptive, decongestant, diuretic, hypoglycemic, hormonal, ophthalmic, hypnotic, sympathomimetic, tranquilizing drugs and vitamins.
22. The composition of claim 1, wherein said active ingredient is selected from furosemide, terfenadine, calcitonin, naproxen, pilocarpine, tetracycline and tetracycline hydrochloride.
- 40 23. A process for preparing a pharmaceutical composition according to claim 1 characterized by the following steps:
  - a) mixing controlled-release microunits with a dry bioadhesive polymer or polymer mixture including at least one bioadhesive polymer;
  - 45 b) dry-compressing the mixture so obtained with the compression force required to bind said dry bioadhesive polymer or polymer mixture to the controlled-release microunits surface;
  - c) crumbling the mass thus obtained so to form granules;
  - d) sieving to obtain particles of the required size.
- 50 24. The process as claimed in claim 23, wherein dry-compressing is effected using a compression force within the range between 0.5 to 8 KN.
25. The process as claimed in claim 23, wherein dry-compression is accomplished by means of a tableting machine or a compaction mill.
- 55 26. The process of claim 23, further comprising including physiologically acceptable extragranular excipients.
27. The process as claimed in claim 23, wherein the size of particles is comprised between 1 and 2,500 micrometers.

Claims for the following Contracting States : ES, GR

1. A process for preparing a controlled-release pharmaceutical composition in the form of bioadhesive granules having the ability of adhering to biologic tissues, said composition comprising
  - a) a multiplicity of controlled-release microunits, containing an active ingredient and at least one component which controls the release of the active ingredient in the environment, said component not substantially contributing to bioadhesive properties of said composition;
  - b) a bioadhesive coating for these microunits, comprising at least one physiologically acceptable bioadhesive polymer, said coating being applied by dry compression on the microunits, which are individually and thoroughly coated with the bioadhesive polymer, said bioadhesive coating being capable of ensuring adhesion of microunits to the tissues or membranes;characterized by the following steps:
  - a) mixing controlled-release microunits with a dry bioadhesive polymer or polymer mixture including at least one bioadhesive polymer;
  - b) dry-compressing the mixture so obtained with the compression force required to bind said dry bioadhesive polymer or polymer mixture to the controlled-release microunits surface;
  - c) crumbling the mass thus obtained so to form granules;
  - d) sieving to obtain particles of the required size.
2. The process according to claim 1, wherein said composition further comprises at least one extragranular physiologically acceptable excipient in contact with the outer surface of the bioadhesive coating.
3. The process according to claim 1, wherein said controlled-release microunits are selected from reservoir units, matrix units, osmotic units, biodegradable units and combination thereof.
4. The process according to claim 1, wherein said controlled-release microunits have a size within the range from 125 to 2,000 micrometers.
5. The process according to claim 4, wherein said range is from 125 to 600 micrometers.
6. The process according to claim 1, wherein said bioadhesive polymer is selected from polyacrylic polymers, acrylic copolymers, cellulose derivatives, natural polymers having bioadhesive properties, and mixtures thereof.
7. The process according to claim 6, wherein the bioadhesive polymer is selected from carbomers, carbomer derivatives, polycarbophil, hydroxypropylmethylcellulose, hydroxyethylcellulose, hydroxypropylcellulose, sodium carboxymethylcellulose, gelatin, sodium alginate, pectin and mixtures thereof.
8. The process according to claim 1, wherein said coating comprises said bioadhesive polymer and a second polymer acting as a binder.
9. The process according to claim 8, wherein the weight ratio of said bioadhesive polymer to said binder is within the range of 0.2 and 20.
10. The process according to claim 9, wherein said range is between 0.5 and 5.
11. The process according to claim 8, wherein the bioadhesive polymer is an acrylic polymer and the binder is a cellulose derivative.
12. The process according to claim 11, wherein said coating is made of mixtures of acrylic polymers and cellulose derivatives selected from mixtures carbomer/hydroxypropyl-methylcellulose, mixtures polycarbophil/hydroxypropyl-methylcellulose and mixtures carbomer/hydroxypropyl-cellulose.
13. The process according to claim 1, wherein the weight ratio of said microunits to the bioadhesive polymer is within the range between 5 and 0.1.
14. The process according to claim 13, wherein said range is between 2.5 and 0.25.

15. The process according to claim 1, wherein the final diameter of the coated microunits is within the range between 1 and 2,500 micrometers.
16. The process of claim 15, wherein said range is between 300 and 600 micrometers.
17. The process according to claim 2, being suitable for oral administration, wherein said excipients comprise at least one hydrophobic agent, which delays hydration of the bioadhesive coating, and at least one disintegrating agent, which promotes dispersion of the bioadhesive microunits over the gastrointestinal mucous membrane.
18. The process according to claim 17, wherein the hydrophobic agent is selected from stearic acid, magnesium stearate, calcium stearate, zinc stearate, talc, glyceryl fumarate, hydrogenated vegetable oils and polyethylene glycols.
19. The process according to claim 17, wherein the disintegrating agent is selected from cross-linked polyvinylpyrrolidone, sodium carboxymethylstarch, sodium croscarmellose, starch, alginic acid, calcium carboxymethylcellulose, guar gum, silicon dioxide and sodium alginate.
20. The process of claim 17, wherein the weight percentage of the hydrophobic agent is within the range of 1 to 10% and that of the disintegrating agent is within the range of 2 to 20%, said weight percentages being based on the weight of the finished product.
21. The process according to claim 1, wherein the active ingredient is selected from analgesic, antibacterial, antibiotic, anticonvulsant, antidepressant, antidiabetic, antifungal, antihistaminic, antihypertensive, anti-inflammatory, antiparkinsonian, antipyretic, anticholinergic, antimicrobial, antiviral, antiulcerative, bronchodilating, cardiovascular, contraceptive, decongestant, diuretic, hypoglycemic, hormonal, ophtalmic, hypnotic, sympathomimetic, tranquillizing drugs and vitamins.
22. The process of claim 1, wherein said active ingredient is selected from furosemide, terfenadine, calcitonin, naproxen, pilocarpine, tetracycline and tetracycline hydrochloride.
23. The process as claimed in claim 1, wherein dry-compressing is effected using a compression force within the range between 0.5 to 8 KN.
24. The process as claimed in claim 1, wherein dry-compression is accomplished by means of a tableting machine or a compaction mill.
25. The process of claim 1, further comprising including physiologically acceptable extragranular excipients.
26. The process as claimed in claim 1, wherein the size of particles is comprised between 1 and 2,500 micrometers.

#### Patentansprüche

Patentansprüche für folgende Vertragsstaaten : AT, BE, CH, LI, DE, DK, FR, GB, IT, LU, MC, NL, PT, SE

1. Pharmazeutische Zusammensetzung mit kontrollierter Freisetzung in Form von bioadhäsiven Granula mit der Fähigkeit zur Anhaftung an biologische Gewebe, wobei die Zusammensetzung umfaßt:
  - a) Eine Vielzahl von Mikroeinheiten mit kontrollierter Freisetzung, enthaltend einen Wirkstoff und mindestens eine Komponente, die die Freisetzung des Wirkstoffes in die Umgebung kontrolliert, wobei die Komponente nicht wesentlich zu den bioadhäsiven Eigenschaften der Zusammensetzung beiträgt;
  - b) einen bioadhäsiven Überzug für diese Mikroeinheiten, umfassend mindestens ein physiologisch verträgliches, bioadhäsives Polymer, wobei der Überzug durch Trockenkompression auf die Mikroeinheiten aufgebracht wird, die einzeln und vollständig mit dem bioadhäsiven Polymer überzogen sind, wobei der bioadhäsive Überzug zur Sicherstellung der Adhäsion der Mikroeinheiten auf den Geweben oder Membranen in der Lage ist.
2. Zusammensetzung nach Anspruch 1, worin die Zusammensetzung ferner mindestens einen extragranulären physiologisch verträglichen Exzipienten in Kontakt mit der äußeren Oberfläche des bioadhäsiven Überzugs umfaßt.

3. Zusammensetzung nach Anspruch 1, worin die Mikroeinheiten mit kontrollierter Freisetzung ausgewählt sind aus Reservoir-Einheiten, Matrix-Einheiten, osmotischen Einheiten, bioabbaubaren Einheiten und Kombinationen davon.
- 5 4. Zusammensetzung nach Anspruch 1, worin die Mikroeinheiten mit kontrollierter Freisetzung eine Größe innerhalb des Bereichs von 125 bis 2.000  $\mu\text{m}$  haben.
5. Zusammensetzung nach Anspruch 4, worin der Bereich von 125 bis 600  $\mu\text{m}$  ist.
- 10 6. Zusammensetzung nach Anspruch 1, worin das bioadhäsive Polymer ausgewählt ist aus Polyacrylsäurepolymeren, Acrylsäurecopolymeren, Cellulosederivaten, natürlichen Polymeren mit bioadhäsiven Eigenschaften und Mischungen davon.
- 15 7. Verfahren nach Anspruch 6, worin das bioadhäsive Polymer ausgewählt ist aus Carbomeren, Carbomerderivaten, Polycarbophil, Hydroxypropylmethylcellulose, Hydroxyethylcellulose, Hydroxypropylcellulose, Natriumcarboxymethylcellulose, Gelatine, Natriumalginat, Pectin und Mischungen davon.
8. Zusammensetzung nach Anspruch 1, worin der Überzug das bioadhäsive Polymer und ein zweites Polymer, das als Binder wirkt, umfaßt.
- 20 9. Zusammensetzung nach Anspruch 8, worin das Gewichtsverhältnis des bioadhäsiven Polymers zu dem Binder innerhalb des Bereichs von 0,2 und 20 liegt.
10. Zusammensetzung nach Anspruch 9, worin der Bereich zwischen 0,5 und 5 ist.
- 25 11. Zusammensetzung nach Anspruch 8, worin das bioadhäsive Polymer ein Acrylsäurepolymer und der Binder ein Cellulosederivat ist.
- 30 12. Zusammensetzung nach Anspruch 11, worin der Überzug hergestellt ist aus Mischungen von Acrylsäurepolymeren und Cellulosederivaten, ausgewählt aus Carbomer/Hydroxypropyl-Methylcellulosemischungen, Polycarbophil/Hydroxypropyl-Methylcellulosemischungen und Carbomer/Hydroxypropyl-Cellulosemischungen.
- 35 13. Zusammensetzung nach Anspruch 1, worin das Gewichtsverhältnis der Mikroeinheiten zum bioadhäsiven Polymer innerhalb des Bereichs zwischen 5 und 0,1 ist.
14. Zusammensetzung nach Anspruch 13, worin der Bereich zwischen 2,5 und 0,25 ist.
- 40 15. Zusammensetzung nach Anspruch 1, worin der Enddurchmesser der überzogenen Mikroeinheiten innerhalb des Bereichs zwischen 1 und 2.500  $\mu\text{m}$  ist.
16. Zusammensetzung nach Anspruch 15, worin der Bereich zwischen 300 und 600  $\mu\text{m}$  ist.
- 45 17. Zusammensetzung nach Anspruch 2, die zur oralen Verabreichung geeignet ist, worin die Exzipienten mindestens ein hydrophobes Mittel umfassen, welches die Hydratation des bioadhäsiven Überzugs inhibiert, und mindestens ein Sprengmittel, welches die Dispersion der bioadhäsiven Mikroeinheiten über die gastrointestinale Schleimhaut fördert.
- 50 18. Zusammensetzung nach Anspruch 17, worin das hydrophobe Mittel ausgewählt ist aus Stearinsäure, Magnesiumstearat, Calciumstearat, Zinkstearat, Talk, Glycerylfumarat, hydrierten pflanzlichen Ölen und Polyethylenglykolen.
19. Zusammensetzung nach Anspruch 17, worin das Sprengmittel ausgewählt ist aus vernetztem Polyvinylpyrrolidon, Natriumcarboxymethylstärke, Natriumcrocarmellose, Stärke, Algininsäure, Calciumcarboxymethylcellulose, Guargummi, Siliciumdioxid und Natriumalginat.
- 55 20. Zusammensetzung nach Anspruch 17, worin der Gewichtsprozentsatz des hydrophoben Mittels innerhalb des Bereichs von 1 bis 10 % und der des Sprengmittels innerhalb des Bereichs von 2 bis 20 % ist, wobei der Gewichtsprozentsatz auf das Gewicht des Endprodukts bezogen ist.

21. Zusammensetzung nach Anspruch 1, worin der Wirkstoff ausgewählt ist aus Analgetika, antibakteriellen Mitteln, Antibiotika, anticonvulsiven Mitteln, Antidepressiva, Antidiabetika, antifungalen Mitteln, Antihistaminika, blutdrucksenkenden Mitteln, entzündungshemmenden Mitteln, Antiparkinson-Mitteln, Antipyretika, Anticholinergika, antimikrobiellen Mitteln, Antivirumitteln, Antiulcermitteln, Bronchodilatoren, kardiovaskulären Mitteln, Kontrazeptiva, Abführmitteln, Diuretika, hypoglykämischen Mitteln, hormonalen Mitteln, Ophthalmika, Hypnotika, Sympathomimetika, tranqulissierenden Arzneimitteln und Vitaminen.

22. Zusammensetzung nach Anspruch 1, worin der Wirkstoff ausgewählt ist aus Furosemid, Terfenadin, Calcitonin, Naproxen, Pilocarpin, Tetracyclin und Tetracyclinhydrochlorid.

23. Verfahren zur Herstellung einer pharmazeutischen Zusammensetzung nach Anspruch 1, **gekennzeichnet** durch die folgenden Schritte:

- a) Mischen von Mikroeinheiten mit kontrollierter Freisetzung mit einem trockenen bioadhäsiven Polymer oder Polymermischung, umfassend mindestens ein bioadhäsives Polymer;
- b) Trockenkomprimierung der so erhaltenen Mischung mit der Kompressionskraft, die zur Bindung des trockenen bioadhäsiven Polymers oder Polymermischung an die Oberfläche der Mikroeinheiten mit kontrollierter Freisetzung erforderlich ist;
- c) Zerkrümeln der so erhaltenen Masse unter Bildung von Granula;
- d) Sieben unter Erhalt von Partikeln der erforderlichen Größe.

24. Verfahren nach Anspruch 23, worin die Trockenkompression erfolgt unter Verwendung einer Kompressionskraft innerhalb des Bereichs zwischen 0,5 bis 8 KN.

25. Verfahren nach Anspruch 23, worin die Trockenkompression erfolgt mittels einer Tablettierungsmaschine oder einer Kompaktionsmühle.

26. Verfahren nach Anspruch 23, das ferner die Aufnahme von physiologisch verträglichen extragranulären Exzipienten umfaßt.

27. Verfahren nach Anspruch 23, worin die Größe der Partikel zwischen 1 und 2.500 µm liegt.

#### Patentansprüche für folgende Vertragsstaaten : ES, GR

1. Verfahren zur Herstellung einer pharmazeutischen Zusammensetzung mit kontrollierter Freisetzung in Form von bioadhäsiven Granula mit der Fähigkeit zur Anhaftung an biologische Gewebe, wobei die Zusammensetzung umfaßt:

- a) Eine Vielzahl von Mikroeinheiten mit kontrollierter Freisetzung, enthaltend einen Wirkstoff und mindestens eine Komponente, die die Freisetzung des Wirkstoffes in die Umgebung kontrolliert, wobei die Komponente nicht wesentlich zu den bioadhäsiven Eigenschaften der Zusammensetzung beiträgt;
- b) einen bioadhäsiven Überzug für diese Mikroeinheiten, umfassend mindestens ein physiologisch verträgliches, bioadhäsives Polymer, wobei der Überzug durch Trockenkompression auf die Mikroeinheiten aufgebracht wird, die einzeln und vollständig mit dem bioadhäsiven Polymer überzogen sind, wobei der bioadhäsive Überzug zur Sicherstellung der Adhäsion der Mikroeinheiten auf den Geweben oder Membranen in der Lage ist;

**gekennzeichnet** durch die folgenden Schritte:

- a) Mischen von Mikroeinheiten mit kontrollierter Freisetzung mit einem trockenen bioadhäsiven Polymer oder Polymermischung, umfassend mindestens ein bioadhäsives Polymer;
- b) Trockenkomprimierung der so erhaltenen Mischung mit der Kompressionskraft, die zur Bindung des trockenen bioadhäsiven Polymers oder Polymermischung an die Oberfläche der Mikroeinheiten mit kontrollierter Freisetzung erforderlich ist;
- c) Zerkrümeln der so erhaltenen Masse unter Bildung von Granula;
- d) Sieben unter Erhalt von Partikeln der erforderlichen Größe.

2. Verfahren nach Anspruch 1, worin die Zusammensetzung ferner mindestens einen extragranulären physiologisch verträglichen Exzipienten in Kontakt mit der äußeren Oberfläche des bioadhäsiven Überzugs umfaßt.

3. Verfahren nach Anspruch 1, worin die Mikroeinheiten mit kontrollierter Freisetzung ausgewählt sind aus Reservoir-Einheiten, Matrix-Einheiten, osmotischen Einheiten, bioabbaubaren Einheiten und Kombinationen davon.
- 5 4. Verfahren nach Anspruch 1, worin die Mikroeinheiten mit kontrollierter Freisetzung eine Größe innerhalb des Bereichs von 125 bis 2.000  $\mu\text{m}$  haben.
5. Verfahren nach Anspruch 4, worin der Bereich von 125 bis 600  $\mu\text{m}$  ist.
- 10 6. Verfahren nach Anspruch 1, worin das bioadhäsive Polymer ausgewählt ist aus Polyacrylsäurepolymeren, Acrylsäurecopolymeren, Cellulosederivaten, natürlichen Polymeren mit bioadhäsiven Eigenschaften und Mischungen davon.
7. Verfahren nach Anspruch 6, worin das bioadhäsive Polymer ausgewählt ist aus Carbomeren, Carbomerderivaten, Polycarbophil, Hydroxypropylmethylcellulose, Hydroxyethylcellulose, Hydroxypropylcellulose, Natriumcarboxymethylcellulose, Gelatine, Natriumalginat, Pectin und Mischungen davon.
- 15 8. Verfahren nach Anspruch 1, worin der Überzug das bioadhäsive Polymer und ein zweites Polymer, das als Binder wirkt, umfaßt.
- 20 9. Verfahren nach Anspruch 8, worin das Gewichtsverhältnis des bioadhäsiven Polymers zu dem Binder innerhalb des Bereichs von 0,2 und 20 liegt.
10. Verfahren nach Anspruch 9, worin der Bereich zwischen 0,5 und 5 ist.
- 25 11. Verfahren nach Anspruch 8, worin das bioadhäsive Polymer ein Acrylsäurepolymer und der Binder ein Cellulosederivat ist.
12. Verfahren nach Anspruch 11, worin der Überzug hergestellt ist aus Mischungen von Acrylsäurepolymeren und Cellulosederivaten, ausgewählt aus Carbomer/Hydroxypropyl-Methylcellulosemischungen, Polycarbophil/Hydroxypropyl-Methylcellulosemischungen und Carbomer/Hydroxypropyl-Cellulosemischungen.
- 30 13. Verfahren nach Anspruch 1, worin das Gewichtsverhältnis der Mikroeinheiten zum bioadhäsiven Polymer innerhalb des Bereichs zwischen 5 und 0,1 ist.
- 35 14. Verfahren nach Anspruch 13, worin der Bereich zwischen 2,5 und 0,25 ist.
15. Verfahren nach Anspruch 1, worin der Enddurchmesser der überzogenen Mikroeinheiten innerhalb des Bereichs zwischen 1 und 2.500  $\mu\text{m}$  ist.
- 40 16. Verfahren nach Anspruch 15, worin der Bereich zwischen 300 und 600  $\mu\text{m}$  ist.
17. Verfahren nach Anspruch 2, die zur oralen Verabreichung geeignet ist, worin die Exzipienten mindestens ein hydrophobes Mittel umfassen, welches die Hydratation des bioadhäsiven Überzugs inhibiert, und mindestens ein Sprengmittel, welches die Dispersion der bioadhäsiven Mikroeinheiten über die gastrointestinale Schleimhaut fördert.
- 45 18. Verfahren nach Anspruch 17, worin das hydrophobe Mittel ausgewählt ist aus Stearinsäure, Magnesiumstearat, Calciumstearat, Zinkstearat, Talk, Glycerylfumarat, hydrierten pflanzlichen Ölen und Polyethylenglykolen.
19. Verfahren nach Anspruch 17, worin das Spengmittel ausgewählt ist aus vernetztem Polyvinylpyrrolidon, Natriumcarboxymethylstärke, Natriumcroscarmellose, Stärke, Algininsäure, Calciumcarboxymethylcellulose, Guargummi, Siliciumdioxid und Natriumalginat.
- 50 20. Verfahren nach Anspruch 17, worin der Gewichtsprozentsatz des hydrophoben Mittels innerhalb des Bereichs von 1 bis 10 % und der des Sprengmittels innerhalb des Bereichs von 2 bis 20 % ist, wobei der Gewichtsprozentsatz auf das Gewicht des Endprodukts bezogen ist.
- 55 21. Verfahren nach Anspruch 1, worin der Wirkstoff ausgewählt ist aus Analgetika, antibakteriellen Mitteln, Antibiotika, anticonvulsiven Mitteln, Antidepressiva, Antidiabetika, antifungalen Mitteln, Antihistaminika, blutdrucksenkenden Mitteln, entzündungshemmenden Mitteln, Antiparkinson-Mitteln, Antipyretika, Anticholinergika, antimikrobiellen

Mitteln, Antivirumitteln, Antiulcermitteln, Bronchodilatoren, cardiovascularen Mitteln, Kontrazeptiva, Abführmitteln, Diuretika, hypoglykämischen Mitteln, hormonalen Mitteln, Ophthalmika, Hypnotika, Sympathomimetika, tranquillisierenden Arzneimitteln und Vitaminen.

- 5 22. Verfahren nach Anspruch 1, worin der Wirkstoff ausgewählt ist aus Furosemid, Terfenadin, Calcitonin, Naproxen, Pilocarpin, Tetracyclin und Tetracyclinhydrochlorid.
23. Verfahren nach Anspruch 1, worin die Trockenkompression erfolgt unter Verwendung einer Kompressionskraft innerhalb des Bereichs zwischen 0,5 bis 8 KN.
- 10 24. Verfahren nach Anspruch 1, worin die Trockenkompression erfolgt mittels einer Tablettierungsmaschine oder einer Kompaktionsmühle.
25. Verfahren nach Anspruch 1, das ferner die Aufnahme von physiologisch verträglichen extragranulären Exzipienten umfaßt.
- 15 26. Verfahren nach Anspruch 1, worin die Größe der Partikel zwischen 1 und 2.500 µm liegt.

# Revendications

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Revendications pour les Etats contractants suivants : AT, BE, CH, LI, DE, DK, FR, GB, IT, LU, MC, NL, PT, SE

1. Composition pharmaceutique à libération retardée sous forme de granulés bioadhésifs ayant la capacité d'adhérer aux tissus biologiques, ladite composition comprenant
  - 25 a) une multiplicité de micro-unités à libération retardée, contenant une substance active et au moins un constituant régulant la libération de la substance active dans l'environnement, ledit constituant ne contribuant pratiquement pas aux propriétés bioadhésives de ladite composition;
  - 30 b) un enrobage bioadhésif pour ces micro-unités, comprenant au moins un polymère bioadhésif physiologiquement acceptable, ledit enrobage étant appliqué par compression à sec sur les micro-unités, qui sont enrobées individuellement et totalement par le polymère bioadhésif, ledit enrobage bioadhésif étant capable d'assurer l'adhérence des micro-unités aux tissus ou aux membranes.
2. Composition selon la revendication 1, dans laquelle ladite composition comprend, en outre, au moins un excipient extragranulaire, physiologiquement acceptable, en contact avec la surface externe de l'enrobage bioadhésif.
3. Composition selon la revendication 1, dans laquelle lesdites micro-unités à libération retardée sont choisies parmi des unités à réservoir, des unités à matrice, des unités osmotiques, des unités biodégradables, et des combinaisons de celles-ci.
4. Composition selon la revendication 1, dans laquelle lesdites micro-unités à libération retardée ont une granulométrie dans la gamme de 125 à 2 000 micromètres.
5. Composition selon la revendication 4, dans laquelle ladite granulométrie est dans la gamme de 125 à 600 micromètres.
6. Composition selon la revendication 1, dans laquelle ledit polymère bioadhésif est choisi parmi les polymères polyacryliques, les copolymères acryliques, les dérivés de cellulose, les polymères naturels ayant des propriétés bioadhésives, et des mélanges de ceux-ci.
7. Composition selon la revendication 6, dans laquelle le polymère bioadhésif est choisi parmi les carbomères, les dérivés de carbomères, le polycarbophile, l'hydroxypropylméthylcellulose, l'hydroxyéthylcellulose, l'hydroxypropylcellulose, la carboxyméthylcellulose sodique, la gélatine, l'alginate de sodium, la pectine, et des mélanges de ceux-ci.
8. Composition selon la revendication 1, dans laquelle ledit enrobage comprenant ledit polymère bioadhésif et un second polymère jouant le rôle de liant.



9. Composition selon la revendication 8, dans laquelle le rapport pondéral dudit polymère bioadhésif audit liant est dans la gamme de 0,2 à 20.
10. Composition selon la revendication 9, dans laquelle ladite gamme est entre 0,5 et 5.
11. Composition selon la revendication 8, dans laquelle le polymère bioadhésif est un polymère acrylique et le liant est un dérivé de cellulose.
12. Composition selon la revendication 11, dans laquelle ledit enrobage est fait de mélanges de polymères acryliques et de dérivés de cellulose choisis parmi les mélanges carbomère/hydroxypropylméthylcellulose, les mélanges polycarbophile/hydroxypropylméthylcellulose et les mélanges carbomère/hydroxypropylcellulose.
13. Composition selon la revendication 1, dans laquelle le rapport pondéral desdites micro-unités au polymère bioadhésif est dans la gamme entre 5 et 0,1.
14. Composition selon la revendication 13, dans laquelle ladite gamme est entre 2,5 et 0,25.
15. Composition selon la revendication 1, dans laquelle le diamètre final des micro-unités enrobées est dans la gamme entre 1 et 2 500 micromètres.
16. Composition selon la revendication 15, dans laquelle ladite gamme est entre 300 et 600 micromètres.
17. Composition selon la revendication 2, convenant à l'administration orale, dans laquelle lesdits excipients comprennent au moins un agent hydrophobe, qui retarde l'hydratation de l'enrobage bioadhésif, et au moins un agent désintégrant, qui favorise la dispersion des micro-unités bioadhésives sur la muqueuse gastro-intestinale.
18. Composition selon la revendication 17, dans laquelle l'agent hydrophobe est choisi parmi l'acide stéarique, le stéarate de magnésium, le stéarate de calcium, le stéarate de zinc, le talc, le fumarate de glycérile, les huiles végétales hydrogénées et les polyéthylèneglycols.
19. Composition selon la revendication 17, dans laquelle l'agent désintégrant est choisi parmi la polyvinylpyrrolidone réticulée, le carboxyméthylamidon sodique, la croscarmellose sodique, l'amidon, l'acide alginique, la carboxyméthylcellulose calcique, la gomme guar, le dioxyde de silicium et l'alginate de sodium.
20. Composition selon la revendication 17, dans laquelle le pourcentage pondéral de l'agent hydrophobe est dans la gamme de 1 à 10% et celui de l'agent désintégrant est dans la gamme de 2 à 20%, lesdits pourcentages pondéraux étant rapportés au poids du produit fini.
21. Composition selon la revendication 1, dans laquelle la substance active est choisie parmi les médicaments analgésiques, antibactériens, antibiotiques, anticonvulsivants, antidépresseurs, antidiabétiques, antifongiques, antihistaminiques, antihypertenseurs, antiinflammatoires, antiparkinsoniens, antipyrétiques, anticholinergiques, antimicrobiens, antiviraux, antiulcéreux, bronchodilatateurs, cardiovasculaires, contraceptifs, décongestionnants, diurétiques, hypoglycémiques, hormonaux, ophtalmiques, hypnotiques, sympathomimétiques, tranquillisants, et les vitamines.
22. Composition selon la revendication 1, dans laquelle ladite substance active est choisie parmi le furosémide, la téfénadine, la calcitonine, le naproxène, la pilocarpine, la tétracycline et le chlorhydrate de tétracycline.
23. Procédé de préparation d'une composition pharmaceutique selon la revendication 1, caractérisé par les étapes suivantes, qui consistent à:
  - a) mélanger les micro-unités à libération retardée avec un polymère bioadhésif sec, ou mélange sec de polymères contenant au moins un polymère bioadhésif;
  - b) comprimer à sec le mélange ainsi obtenu avec la force de compression nécessaire pour lier ledit polymère-bioadhésif sec, ou mélange de polymères, à la surface des micro-unités à libération retardée;
  - c) émietter la masse ainsi obtenue pour former des granules;
  - d) tamiser pour obtenir des particules de granulométrie voulue.

24. Procédé selon la revendication 23, dans lequel la compression à sec est effectuée à l'aide d'une force de compression dans la gamme entre 0,5 et 8 kN.
25. Procédé selon la revendication 23, dans lequel la compression à sec est réalisée au moyen d'une machine à comprimés ou d'un broyeur à compactage.
26. Procédé selon la revendication 23, comprenant, en outre, l'incorporation d'excipients extragranulaires physiologiquement acceptables.
27. Procédé selon la revendication 23, dans lequel la granulométrie des particules est comprise entre 1 et 2 500 micromètres.

**Revendications pour les Etats contractants suivants : ES, GR**

1. Procédé de préparation d'une composition pharmaceutique à libération retardée sous forme de granulés bioadhésifs ayant la capacité d'adhérer aux tissus biologiques, ladite composition comprenant

- a) une multiplicité de micro-unités à libération retardée, contenant une substance active et au moins un constituant régulant la libération de la substance active dans l'environnement, ledit constituant ne contribuant pratiquement pas aux propriétés bioadhésives de ladite composition;
- b) un enrobage bioadhésif pour ces micro-unités, comprenant au moins un polymère bioadhésif physiologiquement acceptable, ledit enrobage étant appliqué par compression à sec sur les micro-unités, qui sont enrobées individuellement et totalement par le polymère bioadhésif, ledit enrobage bioadhésif étant capable d'assurer l'adhérence des micro-unités aux tissus ou aux membranes;

caractérisé par les étapes suivantes, qui consistent à:

- a) mélanger les micro-unités à libération retardée avec un polymère bioadhésif sec, ou mélange sec de polymères contenant au moins un polymère bioadhésif;
- b) comprimer à sec le mélange ainsi obtenu avec la force de compression nécessaire pour lier ledit polymère-bioadhésif sec, ou mélange de polymères, à la surface des micro-unités à libération retardée;
- c) émettre la masse ainsi obtenue pour former des granulés;
- d) tamiser pour obtenir des particules de granulométrie voulue.

2. Procédé selon la revendication 1, dans lequel ladite composition comprend, en outre, au moins un excipient extragranulaire, physiologiquement acceptable, en contact avec la surface externe de l'enrobage bioadhésif.
3. Procédé selon la revendication 1, dans lequel lesdites micro-unités à libération retardée sont choisies parmi des unités à réservoir, des unités à matrice, des unités osmotiques, des unités biodégradables, et des combinaisons de celles-ci.
4. Procédé selon la revendication 1, dans lequel lesdites micro-unités à libération retardée ont une granulométrie dans la gamme de 125 à 2 000 micromètres.
5. Procédé selon la revendication 4, dans lequel ladite granulométrie est dans la gamme de 125 à 600 micromètres.
6. Procédé selon la revendication 1, dans lequel ledit polymère bioadhésif est choisi parmi les polymères polyacryliques, les copolymères acryliques, les dérivés de cellulose, les polymères naturels ayant des propriétés bioadhésives, et des mélanges de ceux-ci.
7. Procédé selon la revendication 6, dans lequel le polymère bioadhésif est choisi parmi les carbomères, les dérivés de carbomères, le polycarbophile/ l'hydroxypropylméthylcellulose/ l'hydroxyéthylcellulose/ l'hydroxypropylcellulose/ la carboxyméthylcellulose sodique, la gélatine, l'alginate de sodium, la pectine, et des mélanges de ceux-ci.
8. Procédé selon la revendication 1, dans lequel ledit enrobage comprenant ledit polymère bioadhésif et un second polymère jouant le rôle de liant.
9. Procédé selon la revendication 8, dans lequel le rapport pondéral dudit polymère bioadhésif audit liant est dans la gamme de 0,2 à 20.

10. Procédé selon la revendication 9, dans lequel ladite gamme est entre 0,5 et 5.
11. Procédé selon la revendication 8, dans lequel le polymère bioadhésif est un polymère acrylique et le liant est un dérivé de cellulose.
12. Procédé selon la revendication 11, dans lequel ledit enrobage est fait de mélanges de polymères acryliques et de dérivés de cellulose choisis parmi les mélanges carbomère/hydroxypropylméthylcellulose, les mélanges polycarbophile/hydroxypropylméthylcellulose et les mélanges carbomère/hydroxypropylcellulose.
13. Procédé selon la revendication 1, dans lequel le rapport pondéral desdites micro-unités au polymère bioadhésif est dans la gamme entre 5 et 0,1.
14. Procédé selon la revendication 13, dans lequel ladite gamme est entre 2,5 et 0,25.
15. Procédé selon la revendication 1, dans lequel le diamètre final des micro-unités enrobées est dans la gamme entre 1 et 2 500 micromètres.
16. Procédé selon la revendication 15, dans lequel ladite gamme est entre 300 et 600 micromètres.
17. Procédé selon la revendication 2, convenant à l'administration orale, dans lequel lesdits excipients comprennent au moins un agent hydrophobe, qui retarde l'hydratation de l'enrobage bioadhésif, et au moins un agent désintégrant, qui favorise la dispersion des micro-unités bioadhésives sur la muqueuse gastro-intestinale.
18. Procédé selon la revendication 17, dans lequel l'agent hydrophobe est choisi parmi l'acide stéarique, le stéarate de magnésium, le stéarate de calcium, le stéarate de zinc, le talc, le fumarate de glycéryle, les huiles végétales hydrogénées et les polyéthylèneglycols.
19. Procédé selon la revendication 17, dans lequel l'agent désintégrant est choisi parmi la polyvinylpyrrolidone réticulée, le carboxyméthylamidon sodique, la croscarmellose sodique, l'amidon, l'acide alginique, la carboxyméthylcellulose calcique, la gomme guar, le dioxyde de silicium et l'alginate de sodium.
20. Procédé selon la revendication 17, dans lequel le pourcentage pondéral de l'agent hydrophobe est dans la gamme de 1 à 10% et celui de l'agent désintégrant est dans la gamme de 2 à 20%, lesdits pourcentages pondéraux étant rapportés au poids du produit fini.
21. Procédé selon la revendication 1, dans lequel la substance active est choisie parmi les médicaments analgésiques, antibactériens, antibiotiques, anticonvulsivants, antidépresseurs, antidiabétiques, antifongiques, antihistaminiques, antihypertenseurs, antiinflammatoires, antiparkinsoniens, antipyrétiques, anticholinergiques, antimicrobiens, antiviraux, antiulcéreux, bronchodilatateurs, cardiovasculaires, contraceptifs, décongestionnants, diurétiques, hypoglycémiques, hormonaux, ophtalmiques, hypnotiques, sympathomimétiques, tranquillisants, et les vitamines.
22. Procédé selon la revendication 1, dans lequel ladite substance active est choisie parmi le furosémide, la terféndine, la calcitonine, le naproxène, la pilocarpine, la tétracycline et le chlorhydrate de tétracycline.
23. Procédé selon la revendication 1, dans lequel la compression à sec est effectuée à l'aide d'une force de compression dans la gamme entre 0,5 et 8 kN.
24. Procédé selon la revendication 1, dans lequel la compression à sec est réalisée au moyen d'une machine à comprimés ou d'un broyeur à compactage.
25. Procédé selon la revendication 1, comprenant, en outre, l'incorporation d'excipients extragranulaires physiologiquement acceptables.
26. Procédé selon la revendication 1, dans lequel la granulométrie des particules est comprise entre 1 et 2 500 micromètres.

